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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,587	10/18/2004	Osamu Cynshi	CYNSHI4	4531
1444 7590 09/07/2007 BROWDY AND NEIMARK, P.L.L.C. 624 NINTH STREET, NW SUITE 300 WASHINGTON, DC 20001-5303			EXAMINER KUDLA, JOSEPH S	
			ART UNIT 1609	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/511,587

Applicant(s)

CYN Shi ET AL.

Examiner

Joseph S. Kudla

Art Unit

1609

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 October 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 8-14 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 10/18/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____.

DETAILED ACTION

Priority

1. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. PCT/JP03/04987, filed on April 18, 2002.

Information Disclosure Statement

2. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

The specification contains reference to articles on page 13, lines 4-8 and lines 11-12 and references to patent documents on page 6, lines 8-10 and lines 16-17.

3. The information disclosure statement filed 10/18/2004 fails to provide an English language translation for two of the prior art references. Specifically, references JP 9-323927 A and JP 6-206842 A are in the Japanese language and have no reference to equivalent English documents. These references have not been considered as to the merits.

Appropriate action is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 8-14 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the amelioration of vascular tone-regulating functionality. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims without undue experimentation to treat the vascular condition induced by diseases such as hypertension, diabetes and arteriosclerosis obliterans as outlined in the claims.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below as seen in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one

Art Unit: 1609

skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

These factors include:

- (A) The breadth of the claims;
- (B) The nature of the invention;
- (C) The state of the prior art;
- (D) The level of one of ordinary skill;
- (E) The level of predictability in the art;
- (F) The amount of direction provided by the inventor;
- (G) The existence of working examples; and
- (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims

The breadth of the instant claims is broad with relation to the ability of the benzofuran compound to improve the vascular tone-relating function of vascular endothelium. The ability to ameliorate or improve the vascular tone-regulating function implies a return of functionality with respect to vasodilation as well as vasoconstriction. Applicant has not provided sufficient evidence to support a claim drawn to the improvement of the vascular tone-regulating function of endothelial cells.

The nature of the invention

Claim 8 is directed to a method for ameliorating the vascular tone-regulating function of vascular endothelium with a benzofuran compound. Claims 9-12 further limit the compound to a specific structure. Claims 13 and 14 recite diseases that could

Art Unit: 1609

induce the condition of where vascular tone-regulating functionality of endothelial cells could be lost.

The state of the prior art

The state of the prior art, although enabling for demonstrating that the benzofuran (4,6-di-t-butyl-5-hydroxy-2, 2- di-n-pentyl-2, 3-dihydrobenzofuran) compound of claim 12 is an effective antioxidant and antihyperlipidemic compound, does not show that the compound has the ability to restore vascular tone-regulating functionality of endothelial cells. Since the Applicant has failed to demonstrate the ability of the benzofuran compound to constrict and dilate the endothelial tissue, Applicant has not taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation.

The level of predictability in the art

The instant claimed invention is highly unpredictable. Many compounds exist in the art that are capable of either vasoconstriction or vasodilation, but no single compound is capable of effectively restoring the functionality of the endothelial tissue. Due to the unpredictability in the pharmaceutical art, it is noted that the invention is required to be assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity. Studies

Art Unit: 1609

conducted by the Applicant as indicated in the specification in examples 1 and 2 shows that the benzofuran compound is effective at protecting the mesenteric artery of the rat from further oxidative damage when treated with oxidized LDL, thus allowing the artery to dilate with a smaller amount of acetylcholine. However, applicant does not show the alternative, vasoconstriction. In addition, it is not clear if the benzofuran is simply protecting or ameliorating the vascular tone-regulating functionality of endothelial cells. It appears that the experiments, as they are shown in the disclosure, show that the benzofuran compound performs as an effective antioxidant. Also, Applicant fails to show how the compound works *in vivo* and how the compound potentiated across species. Therefore, an extrapolation of the data from the rat model to that of any other species is speculation. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. *In re Fisher*, 427 F. 2d, 833, 166 USPQ 18 (CCPA 1970), indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Hence, one of skill in the art is unable to fully predict possible results from the administration of the compound.

The amount of direction provided by the Applicant

The instant specification is not seen to provide adequate guidance, which would allow the skilled artisan to extrapolate from the disclosure and examples provided, to use the claimed method commensurate in the scope with the instant claims. Applicant

Art Unit: 1609

provides limited guidance regarding the use of the instant compound in ameliorating the vascular tone-regulating functionality of endothelial cells. Two *in vitro* examples are shown in the disclosure that at best show the benzofuran compound can perform as an antioxidant. No *in vivo* animal studies or human tissue studies were disclosed where the vascular tone-regulating function was diminished due to diseases such as diabetes or arteriosclerosis obliterans or conditions such as hypertension and then restored or improved.

The specification provides no direction or guidance for determining the administration route, dosages and frequency. With no results, it is difficult to envision that the compounds instantly claimed can treat diminished vascular tone-regulating functionality.

The existence of working examples

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation (*In re Wright*, 999 F. 2d 1557, 1562; 27 USPQ 2d 1510, 1514 (Fed. Cir. 1993)). The specification lacks sufficient disclosure to support applicant's claims of a method for ameliorating the vascular tone-regulating function of vascular endothelium with a benzofuran compound. There is not seen sufficient working examples or data from references on the prior art providing a nexus

Art Unit: 1609

between that which applicant asserts as proof of a method for ameliorating the vascular tone-regulating function of the vascular endothelium. Applicant indicated the mesenteric artery from a rat was collected for the experiment and cut into 2 mm sections for use in the examples. From knowledge of the average size of a rat mesenteric artery and the fact that the tissue samples were tested in eight different environments, the basis of Applicants' findings are based on one to two individual tissue samples tested in each environment. Further, Applicant does not state the age, condition and other specifics of the species.

The quantity of experimentation needed to make and use the invention based on the content of the disclosure

Based on the unpredictable nature of the invention, the state of the prior art, and the breadth of the claims, one skilled in the art could not use the claimed invention without undue experimentation. Reasonable guidance with respect to ameliorating the vascular tone-regulating function of the vascular endothelium relies on quantitative analysis from defined populations which have been successfully pre-screened for this loss in functionality. This type of data might be derived from art accepted animal models that display the condition which applicant asserts would have diminished vascular tone-regulating functionality. The essential element towards the validation of a therapeutic capable of correcting a condition is the ability to test the compound on subjects monitored in advance of these disorders and link those results with subsequent

Art Unit: 1609

histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug treatment and subsequent knowledge of the amelioration of the disease is the essence of verification of a valid therapeutic agent.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 8 recites the limitation "the vascular tone-regulating" in the first line. There is insufficient antecedent basis for this limitation in the claim.

8. Claim 13 recites the limitation "the group" in the fourth line. There is insufficient antecedent basis for this limitation in the claim.

Appropriate action is required.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 8-12 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Miyauchi et al ("Efficacy of a Novel Antioxidant on Vascular Remodeling after Coronary

Art Unit: 1609

Angioplasty: Possible Role of Endothelial Function and Collagen Accumulation,"
Abstracts from Scientific Sessions 2000, II-189).

Miyauchi et al teaches the use of an antioxidant BO-653 (4,6-di-t-butyl-5-hydroxy-2, 2- di-n-pentyl-2, 3-dihydrobenzofuran) (instant claim 12) *in vivo* (7th line of abstract) and *in vitro* that was used to assess the endothelial function (last sentence before conclusion). The conclusion of the study was that BO-653 aided in the recovery (improved/ameliorated) of endothelium-dependent relaxation (conclusion).

11. Claims 8-12 are rejected under 35 U.S.C. 102(a) as being anticipated by Chan et al (J Cardiovasc Pharmacol, vol. 41, no. 6, June 2003, pp. 856-865).

Chan et al teaches a method of administration of a compound BO-653 (4,6-di-t-butyl-5-hydroxy-2, 2- di-n-pentyl-2, 3-dihydrobenzofuran) (instant claim 12) (lower third of abstract) that can block the impairment of endothelial function (first sentence of abstract) of a rat mesenteric artery. Chan et al also teaches that "in vivo studies suggest that antioxidants (such as BO-653) may also have a direct effect of preserving endothelial function" (page 857, paragraph 2, sentence 2).

Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

13. Claims 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Woodman ("Pharmacological approaches to preserving and restoring coronary endothelial function," Expert Opin. Pharmacother., 2001, 2(11)) in view of Takabe et al ("Gene Expression Induced by BO-653, Probucol and BHQ in Human Endothelial Cells," J Atheroscler Thrombosis, vol. 7, no. 4 p.223-230) and further in view of Corsi (US Patent 5,811,457).

Claims 8-14 of the present application state a method of administration of a benzofuran compound that is capable of improving or ameliorating the vascular tone-regulating function of the vascular endothelium. The instant claims 13 and 14 states that the diminished endothelial functional is induced by hypertension, diabetes, arteriosclerosis obliterans and intermittent claudication.

Woodman teaches pharmacological approaches to preserving and restoring endothelial functionality (title). It is taught that one of the pharmacological approaches involves the administration of anti-oxidants (pg 1770, Anti-oxidants section), because "in a number of disease states such as atherosclerosis, hypertension and diabetes, the impairment of endothelium –dependent relaxation has been associated with enhanced degradation of nitric oxide by reactant oxygen species" (Anti-oxidants section, 3rd sentence).

Woodman does not teach the use of the specifically claimed benzofuran compound or that the condition in need of amelioration of the vascular tone-regulating function of the vascular endothelium could be induced by intermittent claudication.

Takabe et al teaches the specific claimed benzofuran compound, 4,6-di-t-butyl-5-hydroxy-2, 2-di-n-pentyl-2, 3-dihydrobenzofuran (BO-653), that acts as a radical scavenging antioxidant that was developed as an anti-atherosclerotic medicine (abstract, 1st sentence).

Corsi teaches intermittent claudication is caused by arteriosclerosis obliterans (column 1, lines 28-32).

It would have been obvious for one having ordinary skill in the art to understand that if endothelial function is disturbed by reactant oxygen species and that if anti-oxidants such as vitamin E and vitamin C were being studied as to their effect at preserving and restoring endothelial functionality, then an alternative antioxidant such as 4,6-di-t-butyl-5-hydroxy-2, 2-di-n-pentyl-2, 3-dihydrobenzofuran, which was developed as an anti-atherosclerotic medicine, would be capable of addressing the same issue. In addition, atherosclerosis, a common form of arteriosclerosis, is a hardening of the arteries. During the hardening phase, plaques are deposited on the walls of the arteries which cause occlusions or narrowing. It is this narrowing of the peripheral arteries which is called arteriosclerosis obliterans. Because it is known to one having ordinary skill in the art as well as taught by Corsi, it would be obvious that if one had the condition of intermittent claudication, the application of the benzofuran derivative which would treat atherosclerosis, hence arteriosclerosis (which includes arteriosclerosis obliterans), would treat intermittent claudication also.

The references thus provide ample motivation and direction with respect to the use of an antioxidant to preserve and restore endothelial functionality. In the instant

Art Unit: 1609

case, the administration of an amount of a benzofuran to a patient having diabetes, atherosclerosis and hypertension would also improve the vascular tone-regulating function of the vascular endothelium for someone having conditions such as arteriosclerosis obliterans and intermittent claudication as well.

The combined references thus provide the teaching, suggestion, and motivation to administer an antioxidant such as 4,6-di-*t*-butyl-5-hydroxy-2, 2-di-*n*-pentyl-2, 3-dihydrobenzofuran as a method of ameliorating the vascular tone-regulating function of the vascular endothelium. Accordingly, the claims are deemed properly rejected as being anticipated by Woodman in view of Takabe et al in further view of Corsi.

No Claims Allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph S. Kudla whose telephone number is (571) 270-3288. The examiner can normally be reached on 9am-5pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Art Unit: 1609

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

JK



JEFFREY STUCKER
SUPERVISORY PATENT EXAMINER